

# PROTONIX<sup>®</sup>

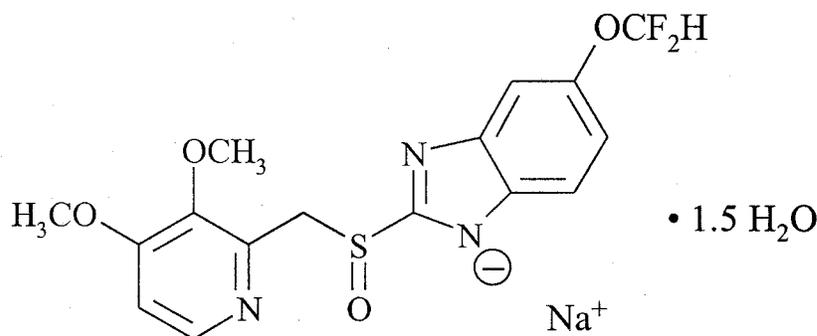
(pantoprazole sodium)

Delayed-Release Tablets

R<sub>x</sub> only

## DESCRIPTION

The active ingredient in PROTONIX<sup>®</sup> (pantoprazole sodium) Delayed-Release Tablets is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is C<sub>16</sub>H<sub>14</sub>F<sub>2</sub>N<sub>3</sub>NaO<sub>4</sub>S x 1.5 H<sub>2</sub>O, with a molecular weight of 432.4. The structural formula is:



Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane.

The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8.

PROTONIX is supplied as a delayed-release tablet for oral administration, available in 2 strengths. Each delayed-release tablet contains 45.1 mg or 22.6 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg or 20 mg pantoprazole, respectively) with the following inactive ingredients: calcium stearate, crospovidone, hypromellose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate.

## CLINICAL PHARMACOLOGY

### Pharmacokinetics

PROTONIX is prepared as an enteric-coated tablet so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (C<sub>max</sub>) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous

doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers (see Metabolism section) with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole tablet, the peak concentration ( $C_{max}$ ) is 2.5  $\mu\text{g/mL}$ , the time to reach the peak concentration ( $t_{max}$ ) is 2.5 h and the total area under the plasma concentration versus time curve (AUC) is 4.8  $\mu\text{g}\cdot\text{hr/mL}$ . When pantoprazole is given with food, its  $t_{max}$  is highly variable and may increase significantly. Following intravenous administration of pantoprazole to extensive metabolizers, its total clearance is 7.6-14.0 L/h and its apparent volume of distribution is 11.0-23.6L.

### **Absorption**

The absorption of pantoprazole is rapid, with a  $C_{max}$  of 2.5  $\mu\text{g/mL}$  that occurs approximately 2.5 hours after single or multiple oral 40-mg doses. Pantoprazole is well absorbed; it undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of pantoprazole with food may delay its absorption up to 2 hours or longer; however, the  $C_{max}$  and the extent of pantoprazole absorption (AUC) are not altered. Thus, pantoprazole may be taken without regard to timing of meals.

### **Distribution**

The apparent volume of distribution of pantoprazole is approximately 11.0-23.6L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

### **Metabolism**

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation ( $\leq 23\%$ ) with once daily dosing.

### **Elimination**

After a single oral or intravenous dose of  $^{14}\text{C}$ -labeled pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

## **Special Populations**

### ***Geriatric***

Only slight to moderate increases in pantoprazole AUC (43%) and  $C_{max}$  (26%) were found in elderly volunteers (64 to 76 years of age) after repeated oral administration, compared with younger subjects. No dosage adjustment is recommended based on age.

### ***Pediatric***

The pharmacokinetics of pantoprazole have not been investigated in patients <18 years of age.

### ***Gender***

There is a modest increase in pantoprazole AUC and  $C_{max}$  in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is needed based on gender (Also see **Use in Women**).

### ***Renal Impairment***

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

### ***Hepatic Impairment***

In patients with mild to severe hepatic impairment, maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in slow CYP2C19 metabolizers, where no dosage frequency adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once daily multiple-dose administration. No dosage adjustment is needed in patients with mild to severe hepatic impairment. Doses higher than 40 mg/day have not been studied in hepatically-impaired patients.

## **Drug-Drug Interactions**

Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6 and 2C9. In *in vivo* drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and phenytoin [also a CYP3A4 inducer]), nifedipine, midazolam, and clarithromycin (CYP3A4 substrates), metoprolol (a CYP2D6 substrate), diclofenac (a CYP2C9 substrate) and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9 and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. *In vivo* studies also suggest that pantoprazole does not significantly affect the kinetics of other drugs (cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, warfarin, metoprolol, nifedipine, carbamazepine, midazolam, clarithromycin, and oral contraceptives) metabolized by CYPs 2C19, 3A4, 2C9, 2D6 and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are co-administered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole. Although no significant drug-drug interactions have been observed in clinical studies, the potential for significant drug-drug interactions with more than

once daily dosing with high doses of pantoprazole has not been studied in poor metabolizers or individuals who are hepatically impaired.

## **Pharmacodynamics**

### ***Mechanism of Action***

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H<sup>+</sup>,K<sup>+</sup>)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H<sup>+</sup>,K<sup>+</sup>)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested.

### ***Antisecretory Activity***

Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20-80 mg) or a single dose of intravenous (20-120 mg) pantoprazole in healthy volunteers. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once a day dosing for 7 days the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

In a series of dose-response studies pantoprazole, at oral doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric pH and in the percent of time gastric pH was > 3 and > 4. Treatment with 40 mg of pantoprazole produced optimal increases in gastric pH which were significantly greater than the 20-mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH. The effects of pantoprazole on median pH from one double-blind crossover study are shown below.

### **Effect of Single Daily Doses of Oral Pantoprazole on Intra-gastric pH**

Time	Median pH on day 7			
	Placebo	20 mg	40 mg	80 mg
8 a.m. - 8 a.m. (24 hours)	1.3	2.9*	3.8*#	3.9*#
8 a.m. - 10 p.m. (Daytime)	1.6	3.2*	4.4*#	4.8*#
10 p.m. - 8 a.m. (Nighttime)	1.2	2.1*	3.0*	2.6*

\* Significantly different from placebo

# Significantly different from 20 mg

### ***Serum Gastrin Effects***

Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of erosive esophagitis (EE) in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of PROTONIX for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the 10, 20, and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8 week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole dose groups. Median serum gastrin levels remained within normal limits during maintenance therapy with PROTONIX (pantoprazole sodium) Delayed-Release Tablets.

In long-term international studies involving over 800 patients, a 2- to 3-fold mean increase from the pretreatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials.

Following healing of gastric or duodenal ulcers with pantoprazole treatment, elevated gastrin levels return to normal by at least 3 months.

### ***Enterochromaffin-Like (ECL) Cell Effects***

In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving 40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density starting after the first year of use which appeared to plateau after 4 years.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin concentrations. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by proton pump inhibitors. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery. (See **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**).

### ***Other Effects***

No clinically relevant effects of pantoprazole on cardiovascular, respiratory, ophthalmic, or central nervous system function have been detected. In a clinical pharmacology study, pantoprazole 40 mg given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin and growth hormone.

In a 1-year study of GERD patients treated with pantoprazole 40 mg or 20 mg, there were no changes from baseline in overall levels of T3, T4, and TSH.

## Clinical Studies

PROTONIX Delayed-Release Tablets were used in all clinical trials.

### Erosive Esophagitis (EE) Associated with Gastroesophageal Reflux Disease (GERD)

A U.S. multicenter double-blind, placebo-controlled study of PROTONIX 10 mg, 20 mg, or 40 mg once daily was conducted in 603 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above (Hetzel-Dent scale). In this study, approximately 25% of enrolled patients had severe EE of grade 3 and 10% had grade 4. The percentages of patients healed (per protocol, n=541) in this study were as follows:

#### Erosive Esophagitis Healing Rates (per protocol)

Week	PROTONIX			Placebo (n = 68)
	10 mg QD (n = 153)	20 mg QD (n = 158)	40 mg QD (n = 162)	
4	45.6% <sup>+</sup>	58.4% <sup>+#</sup>	75.0% <sup>+*</sup>	14.3%
8	66.0% <sup>+</sup>	83.5 % <sup>+#</sup>	92.6% <sup>+*</sup>	39.7%

<sup>+</sup> (p < 0.001) PROTONIX versus placebo.

<sup>\*</sup> (p < 0.05) versus 10 mg, or 20 mg PROTONIX

<sup>#</sup> (p < 0.05) versus 10 mg PROTONIX

In this study, all PROTONIX treatment groups had significantly greater healing rates than the placebo group. This was true regardless of *H. pylori* status for the 40-mg and 20-mg PROTONIX treatment groups. The 40-mg dose of PROTONIX resulted in healing rates significantly greater than those found with either the 20- or 10-mg dose.

A significantly greater proportion of patients taking PROTONIX 40 mg experienced complete relief of daytime and nighttime heartburn and the absence of regurgitation starting from the first day of treatment compared with placebo. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking placebo.

PROTONIX 40 mg and 20 mg once daily were also compared with nizatidine 150 mg twice daily in a U.S. multicenter, double-blind study of 243 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above. The percentages of patients healed (per protocol, n=212) were as follows:

#### Erosive Esophagitis Healing Rates (per protocol)

Week	PROTONIX		Nizatidine 150 mg BID (n = 70)
	20 mg QD (n = 72)	40 mg QD (n = 70)	
4	61.4% <sup>+</sup>	64.0% <sup>+</sup>	22.2%
8	79.2% <sup>+</sup>	82.9 % <sup>+</sup>	41.4%

<sup>+</sup> (p < 0.001) PROTONIX versus nizatidine.

Once daily treatment with PROTONIX 40 or 20 mg resulted in significantly superior rates of healing at both 4 and 8 weeks compared with twice daily treatment with 150 mg of nizatidine. For the 40 mg treatment group, significantly greater healing rates compared to nizatidine were achieved regardless of the *H. pylori* status.

A significantly greater proportion of the patients in the PROTONIX treatment groups experienced complete relief of nighttime heartburn and regurgitation starting on the first day and of daytime heartburn on the second day compared with those taking nizatidine 150 mg twice daily. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking nizatidine.

### Long-Term Maintenance of Healing of Erosive Esophagitis

Two independent, multicenter, randomized, double-blind, comparator-controlled trials of identical design were conducted in GERD patients with endoscopically-confirmed healed erosive esophagitis to demonstrate efficacy of PROTONIX in long-term maintenance of healing. The two U.S. studies enrolled 386 and 404 patients, respectively, to receive either 10 mg, 20 mg, or 40 mg of PROTONIX (pantoprazole sodium) Delayed-Release Tablets once daily or 150 mg of ranitidine twice daily. As demonstrated in the table below, PROTONIX 40 mg and 20 mg were significantly superior to ranitidine at every time point with respect to the maintenance of healing. In addition, PROTONIX 40 mg was superior to all other treatments studied.

#### Long-Term Maintenance of Healing of Erosive Gastroesophageal Reflux Disease (GERD Maintenance): Percentage of Patients Who Remained Healed

	PROTONIX 20 mg QD	PROTONIX 40 mg QD	Ranitidine 150 mg BID
<b>Study 1</b>	n = 75	n = 74	n = 75
Month 1	91*	99*	68
Month 3	82*	93*#	54
Month 6	76*	90*#	44
Month 12	70*	86*#	35
<b>Study 2</b>	n = 74	n = 88	n = 84
Month 1	89*	92*#	62
Month 3	78*	91*#	47
Month 6	72*	88*#	39
Month 12	72*	83*	37

\* (p < 0.05 vs ranitidine)

# (p < 0.05 vs PROTONIX 20 mg)

Note: PROTONIX 10 mg was superior (p < 0.05) to ranitidine in study 2 but not study 1.

PROTONIX 40 mg was superior to ranitidine in reducing the number of daytime and nighttime heartburn episodes from the first through the twelfth month of treatment. PROTONIX 20 mg, administered once daily, was also effective in reducing episodes of daytime and nighttime heartburn in one trial.

### Number of Episodes of Heartburn (mean ± SD)

		PROTONIX 40 mg QD	Ranitidine 150 mg BID
Month 1	Daytime	5.1 ± 1.6*	18.3 ± 1.6
	Nighttime	3.9 ± 1.1*	11.9 ± 1.1
Month 12	Daytime	2.9 ± 1.5*	17.5 ± 1.5
	Nighttime	2.5 ± 1.2*	13.8 ± 1.3

\* (p < 0.001 vs ranitidine, combined data from the 2 U.S. studies)

#### **Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome**

In a multicenter, open-label trial of 35 patients with pathological hypersecretory conditions, such as Zollinger-Ellison syndrome with or without multiple endocrine neoplasia-type I, PROTONIX successfully controlled gastric acid secretion. Doses ranging from 80 mg daily to 240 mg daily maintained gastric acid output below 10mEq/h in patients without prior acid-reducing surgery and below 5 mEq/h in patients with prior acid-reducing surgery.

Doses were initially titrated to the individual patient needs, and adjusted in some patients based on the clinical response with time. (See DOSAGE AND ADMINISTRATION.) PROTONIX was well tolerated at these dose levels for prolonged periods (greater than 2 years in some patients).

#### **INDICATIONS AND USAGE**

##### **Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)**

PROTONIX<sup>®</sup> (pantoprazole sodium) Delayed-Release Tablets are indicated for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis. For those patients who have not healed after 8 weeks of treatment, an additional 8 week course of PROTONIX may be considered.

##### **Maintenance of Healing of Erosive Esophagitis**

PROTONIX Delayed-Release Tablets are indicated for maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with gastroesophageal reflux disease (GERD). Controlled studies did not extend beyond 12 months.

##### **Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome**

PROTONIX Delayed-Release Tablets are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

#### **CONTRAINDICATIONS**

PROTONIX Delayed-Release Tablets are contraindicated in patients with known hypersensitivity to any component of the formulation.

## **PRECAUTIONS**

### **General**

Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy.

Owing to the chronic nature of erosive esophagitis, there may be a potential for prolonged administration of pantoprazole. In long-term rodent studies, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown.

Generally, daily treatment with any acid-suppressing medications over a long period of time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin (Vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This possibility should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

### **Information for Patients**

Patients should be cautioned that PROTONIX Delayed-Release Tablets should not be split, crushed or chewed. The tablets should be swallowed whole, with or without food in the stomach. Concomitant administration of antacids does not affect the absorption of pantoprazole.

### **Drug Interactions**

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of pantoprazole with other drugs, no dosage adjustment is needed with concomitant use of the following: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin, midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when co-administered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids.

Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis, of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day.

In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

A 26-week p53 +/- transgenic mouse carcinogenicity study was not positive.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* AS52/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

## **Pregnancy**

### ***Teratogenic Effects***

#### ***Pregnancy Category B***

Teratology studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to 40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

### **Nursing Mothers**

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

### **Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

### **Use in Women**

Erosive esophagitis healing rates in the 221 women treated with PROTONIX (pantoprazole sodium) Delayed-Release Tablets in U.S. clinical trials were similar to those found in men. In the 122 women treated long-term with PROTONIX 40 mg or 20 mg, healing was maintained at a rate similar to that in men. The incidence rates of adverse events were also similar for men and women.

### **Use in Elderly**

In short-term U.S. clinical trials, erosive esophagitis healing rates in the 107 elderly patients ( $\geq 65$  years old) treated with PROTONIX were similar to those found in patients under the age of 65. The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

### **Laboratory Tests**

There have been reports of false-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving pantoprazole.

### **ADVERSE REACTIONS**

Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

In two U.S. controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following adverse events considered by investigators to be possibly, probably or definitely related to drug occurred in 1% or more in the individual studies of GERD patients on therapy with PROTONIX.

**Most Frequent Adverse Events Reported as Drug Related in  
Short-term Domestic Trials**

Study Event	% Incidence			
	Study 300-US		Study 301-US	
	PROTONIX (n = 521)	Placebo (n = 82)	PROTONIX (n = 161)	Nizatidine (n = 82)
Headache	6	6	9	13
Diarrhea	4	1	6	6
Flatulence	2	2	4	0
Abdominal pain	1	2	4	4
Rash	<1	0	2	0
Eructation	1	1	0	0
Insomnia	<1	2	1	1
Hyperglycemia	1	0	<1	0

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In international short-term double-blind or open-label, clinical trials involving 20 to 80 mg per day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks.

**Adverse Events in GERD Patients in Short-term International Trials**

Study Event	% Incidence			
	Pantoprazole Total (N=2805)	Ranitidine 300 mg (N=594)	Omeprazole 20 mg (N=474)	Famotidine 40 mg (N=239)
	Headache	2	3	2
Diarrhea	2	2	2	<1
Abdominal Pain	1	1	<1	<1

In two U.S. controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 12 months, the following adverse events considered by investigators to be possibly, probably or definitely related to drug occurred in 1% or more of GERD patients on long-term therapy.

**Most Frequent Adverse Events Reported as Drug Related in  
Long-term Domestic Trials**

Study Event	% Incidence	
	PROTONIX (n = 536)	Ranitidine (n = 185)
Headache	5	2
Abdominal pain	3	1
Liver function tests abnormal	2	<1
Nausea	2	2
Vomiting	2	2

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short- and long-term domestic and international trials, the following treatment-emergent events, regardless of causality, occurred at a rate of  $\geq 1\%$  in pantoprazole-treated patients: anxiety, arthralgia, asthenia, back pain, bronchitis, chest pain, constipation, cough increased, dizziness, dyspepsia, dyspnea, flu syndrome, gastroenteritis, gastrointestinal disorder, hyperlipemia, hypertonia, infection, liver function tests abnormal, migraine, nausea, neck pain, pain, pharyngitis, rectal disorder, rhinitis, SGPT increased, sinusitis, upper respiratory tract infection, urinary frequency, urinary tract infection, and vomiting.

Additional treatment-emergent adverse experiences occurring in  $<1\%$  of pantoprazole-treated patients from these trials are listed below by body system. In most instances the relationship to pantoprazole was unclear.

**BODY AS A WHOLE:** abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, non-specified drug reaction, photosensitivity reaction.

**CARDIOVASCULAR SYSTEM:** abnormal electrocardiogram, angina pectoris, arrhythmia, atrial fibrillation/flutter, cardiovascular disorder, chest pain substernal, congestive heart failure, hemorrhage, hypertension, hypotension, myocardial infarction, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

**DIGESTIVE SYSTEM:** anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

**ENDOCRINE SYSTEM:** diabetes mellitus, glycosuria, goiter.

**HEPATO-BILIARY SYSTEM:** biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

**HEMIC AND LYMPHATIC SYSTEM:** anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

**METABOLIC AND NUTRITIONAL:** dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

**MUSCULOSKELETAL SYSTEM:** arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

**NERVOUS SYSTEM:** abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, neuropathy, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

**RESPIRATORY SYSTEM:** asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

**SKIN AND APPENDAGES:** acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pruritus, skin disorder, skin ulcer, sweating, urticaria.

**SPECIAL SENSES:** abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

**UROGENITAL SYSTEM:** albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

In an open-label US clinical trial conducted in 35 patients with pathological hypersecretory conditions treated with PROTONIX for up to 27 months, the adverse events reported were consistent with the safety profile of the drug in other populations.

### **Postmarketing Reports**

There have been spontaneous reports of adverse events with the postmarketing use of pantoprazole. These reports include anaphylaxis (including anaphylactic shock); angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; interstitial nephritis; pancreatitis; pancytopenia; and rhabdomyolysis. In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

### **Laboratory Values**

In two U.S. controlled, short-term trials in patients with erosive esophagitis associated with GERD, 0.4 % of the patients on PROTONIX 40 mg experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. In two U.S. controlled, long-term trials in patients with erosive esophagitis associated with GERD, none of 178 patients (0%) on PROTONIX 40 mg and two of 181 patients (1.1%) on PROTONIX 20 mg, experienced significant transaminase elevations at 12 months (or earlier if a patient discontinued prematurely). Significant elevations of SGOT or SGPT were defined as values at least three times the upper limit of normal that were non-sporadic and had no clear alternative explanation. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

### **OVERDOSAGE**

Experience in patients taking very high doses of pantoprazole is limited. There have been spontaneous reports of overdosage with pantoprazole, including a suicide in which pantoprazole 560 mg and undetermined amounts of chloroquine and zopiclone were also ingested. There have also been spontaneous reports of patients taking similar amounts of pantoprazole (400 and 600 mg) with no adverse effects.

Pantoprazole is not removed by hemodialysis. In case of overdose, treatment should be symptomatic and supportive.

Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg and 887 mg/kg were lethal to mice, rats and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

## **DOSAGE AND ADMINISTRATION**

### **Treatment of Erosive Esophagitis**

The recommended adult oral dose is 40 mg given once daily for up to 8 weeks. For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered. (See **INDICATIONS AND USAGE**.)

### **Maintenance of Healing of Erosive Esophagitis**

The recommended adult oral dose is one PROTONIX 40 mg Delayed-Release Tablet, taken daily. (See **Clinical Studies**.)

### **Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome**

The dosage of PROTONIX in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult starting dose is 40 mg twice daily. Dosage regimens should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 240 mg daily have been administered. Some patients have been treated continuously with PROTONIX for more than 2 years.

No dosage adjustment is necessary in patients with renal impairment, hepatic impairment, or for elderly patients. Doses higher than 40 mg/day have not been studied in hepatically-impaired patients. No dosage adjustment is necessary in patients undergoing hemodialysis.

PROTONIX delayed-release Tablets should be swallowed whole, with or without food in the stomach. If patients are unable to swallow a 40 mg tablet, two 20 mg tablets may be taken. Concomitant administration of antacids does not affect the absorption of PROTONIX.

Patients should be cautioned that PROTONIX delayed-release Tablets should not be split, chewed or crushed.

## **HOW SUPPLIED**

PROTONIX<sup>®</sup> (pantoprazole sodium) Delayed-Release Tablets are supplied as 40 mg yellow oval biconvex delayed-release tablets imprinted with PROTONIX (brown ink) on one side.

They are available as follows:

NDC 0008-0841-10 bottles of 100

NDC 0008-0841-81 bottles of 90

NDC 0008-0841-91 bottles of 1000

NDC 0008-0841-99 carton of 10 Redipak<sup>®</sup> blister strips of 10 tablets each

PROTONIX is supplied as 20 mg yellow oval biconvex delayed-release tablets imprinted with P20 (brown ink) on one side.

They are available as follows:

NDC 0008-0843-81 bottles of 90

**Storage**

Store PROTONIX<sup>®</sup> delayed-release Tablets at 20°–25°C (68°–77°F); excursions permitted to 15°–30°C (59°–86°F).

[See USP Controlled Room Temperature].

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